REMARKS

Claims 1, 3, 7-20, 22, and 37 are pending in the application. No amendments have been made by the present response.

35 U.S.C. § 103(a)

On pages 2-3 of the Office Action, claims 1, 3, 7, 9, 12-15, 17-19, 22, and 37 were finally rejected as allegedly unpatentable over Cordell et al., WO 91/04339 ("Cordell"), Patino et al. (1996) Science 273:622-26 ("Patino"), Hughes et al. (1996) Proc. Natl. Acad. Sci. USA 93:2065-70 ("Hughes"), Rieger et al. (1997) Nat. Med. 12(3):1383-88 ("Rieger"), Hitzeman et al., U.S. Patent No. 4,775,622 ("Hitzeman"), and Chang et al., U.S. Patent No. 5,010,003 ("Chang").

This rejection was discussed during the telephone interview of March 6, 2007. No agreement was reached during that discussion. However, the Examiner suggested that applicant file an after-final response that emphasizes the arguments made to date so that the Examiner will have an opportunity to give further consideration to applicant's position.

Independent claim 1 is directed to a method of identifying a candidate substance that inhibits aggregation of a mammalian aggregate-prone amyloid protein in a yeast cell. The claimed method includes the following steps: (a) contacting a yeast cell that expresses a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide with a candidate substance under conditions effective to allow aggregated amyloid formation in the yeast cell; and (b) determining the ability of the candidate substance to inhibit the aggregation of the aggregate-prone amyloid protein in the yeast cell.

Cordell describes methods of screening to identify agents that can reduce preamyloid aggregate formation. Cordell does not describe an assay that uses a yeast host cell expressing a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide to evaluate candidate substances for their ability to inhibit the aggregation of the aggregate-prone amyloid protein in the yeast cell.

As discussed in the telephone interview, the present application was previously finally rejected (on different grounds than those in the current Office Action) and all of the prior rejections were reversed by the Board in a decision dated February 27, 2004 (including an

anticipation rejection based on Cordell). As noted in the present Office Action and in the telephone interview with the Examiner, the Board's decision made a concluding remark (under the heading "Other Issue") that "[i]n view of the discussion above regarding the Cordell reference, the examiner should determine whether the disclosure of Cordell would render obvious the claimed method, alone or in combination with an appropriate secondary reference." This statement by the Board was a mere suggestion to the Examiner to consider the question of obviousness. It took no stance whatsoever on what the outcome of that analysis should be (which of course it cannot do since that issue was not presented to the Board). Furthermore, applicant emphasizes the claims that are currently pending in the application are not identical to those that were reviewed by the Board. Subsequent to the appeal, applicant amended the claims to clarify that the claimed method identifies substances that inhibit the aggregation of an aggregate-prone amyloid protein "in a yeast cell."

As noted above, the Board concluded that Cordell does not anticipate the claimed methods. Applicant respectfully submits that Patino, Hughes, Rieger, Hitzeman, and Chang do not suggest modifying the methods of Cordell to arrive at the claimed invention. In particular, none of the secondary references taken alone or in combination suggests that a yeast cell can be used to screen for substances that inhibit aggregation of a mammalian aggregate-prone amyloid protein in the yeast cell.

Patino describes the aggregation of the yeast protein Sup35 in yeast cells in a manner that depends upon the concentration and functional state of the chaperone protein Hsp104. Nowhere does Patino describe or suggest that a mammalian aggregate-prone amyloid protein would form aggregates upon expression in yeast cells. This distinction was acknowledged in the prior Office Action, which stated at page 5 that "the aggregate-prone amyloid peptide [of Patino] is not mammalian."

Hughes describes the use of a yeast two-hybrid system to study the interaction of two β-amyloid (Aβ) peptide monomers. Hughes describes Aβ monomer interaction, but nowhere describes aggregated amyloid formation of Aβ expressed in yeast cells. To the contrary, Hughes concludes that the "[r]esults presented in Fig. 4 also suggest that no covalent higher-order bait-prey aggregates can be observed on the gel. This system may therefore provide an opportunity to freeze-frame the monomer-monomer interaction" (page 2070; emphasis added).

The claimed methods assess the ability of a candidate substance to inhibit the aggregation of a mammalian aggregate-prone amyloid protein in a yeast cell. Because Hughes concludes that the bait-Aβ and prey-Aβ proteins do not form aggregates when expressed in yeast cells, Hughes actually teaches away from the claimed methods.

Rieger describes the use of a yeast two-hybrid system to detect an interaction between the prion protein PrP and laminin receptor precursor (LRP). Rieger nowhere describes or suggests that PrP forms aggregates when expressed in the yeast cell. Rieger's description of an interaction between PrP and LRP when expressed in yeast would not have led the person of ordinary skill in the art to expect that PrP or any other mammalian aggregate-prone amyloid protein would form aggregates when expressed in yeast.

Hitzeman describes transformation of yeast with an expression vector encoding a polypeptide containing a signal sequence and a heterologous protein, such that the signal sequence results in secretion of the heterologous protein from the yeast. Chang also describes methods of secreting a heterologous protein from yeast. Because the proteins of Hitzeman and Chang are described as being secreted, the skilled person would have had no reason to expect that yeast that produce such secreted proteins could or should be used to evaluate aggregation of the proteins within the cell. There is no evidence of record to suggest that such an aggregation event would occur or that the skilled person, at the time the present application was filed, would have had any reason to screen for aggregation (in a yeast cell) of a protein that contains a sequence intended to cause its secretion.

As detailed above, none of the secondary references disclose or suggest that a mammalian aggregate-prone amyloid peptide forms aggregates when expressed in a yeast cell. The cited references either do not address the subject of aggregation of such a peptide or suggest that aggregation does not occur when a mammalian aggregate-prone amyloid peptide is expressed in yeast (see the comments above regarding Hughes, which states that the Aβ peptide did not form aggregates when expressed in yeast). The Office Action's remark at page 3 that "yeast cells represent an excellent well-known cellular model to study protein-protein interactions" does not overcome the failure of the cited references to suggest that a mammalian aggregate-prone amyloid peptide would form aggregates when expressed in a yeast cell. Because none of the secondary references taken alone or in combination suggests that a yeast

cell can be used to screen for a substance that inhibits aggregation of a mammalian aggregate-prone amyloid protein in the yeast cell, these references fail to cure the deficiencies of Cordell.

In light of these comments, applicant respectfully submits that the combination of Cordell, Patino, Hughes, Rieger, Hitzeman, and Chang does not render the claimed invention obvious and therefore request that the Examiner withdraw the rejection of independent claim 1 and dependent claims 3, 7, 9, 12-15, 17-19, 22, and 37.

On page 4 of the Office Action, dependent claims 8, 17, 18, and 20 were finally rejected as allegedly unpatentable over Cordell, Patino, Hughes, Rieger, Hitzeman, and Chang as set forth above and further in view of Chalfie et al. (1994) Science 263:802-05 ("Chalfie").

The Office Action cited Chalfie as allegedly describing the use of green fluorescent protein as a marker for gene expression and asserted that the skilled artisan would have been motivated to use green fluorescent protein to monitor protein aggregation in yeast cell culture media.

As detailed above, the combination of Cordell, Patino, Hughes, Rieger, Hitzeman, and Chang does not render obvious the method of independent claim 1. Chalfie provides nothing that supplements the deficiencies of Cordell, Patino, Hughes, Rieger, Hitzeman, and Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claims 8, 17, 18, and 20 should also be in condition for allowance.

On page 4 of the Office Action, dependent claims 7, 10, and 11 were finally rejected as allegedly unpatentable over Cordell, Patino, Hughes, Rieger, Hitzeman, and Chang as set forth above and further in view of Tikhonenko et al. (1995) Oncogene 11:1499-508 ("Tikhonenko").

The Office Action cited Tikhonenko as allegedly describing the use of the glucocorticoid receptor element as a marker for protein inducible expression and asserted that the skilled artisan would have been motivated to modify the fusion proteins of Cordell to use the glucocorticoid receptor to monitor and induce protein expression in a cell culture assay.

As detailed above, the combination of Cordell, Patino, Hughes, Rieger, Hitzeman, and Chang does not render obvious the method of independent claim 1. Tikhonenko provides nothing that supplements the deficiencies of Cordell, Patino, Hughes, Rieger, Hitzeman, and

Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claims 7, 10, and 11 should also be in condition for allowance.

On page 5 of the Office Action, dependent claim 16 was finally rejected as allegedly unpatentable over Cordell, Patino, Hughes, Rieger, Hitzeman, and Chang as set forth above and further in view of Nordstedt et al. (1994) J. Biol. Chem. 49:30773-76 ("Nordstedt").

The Office Action cited Nordstedt as allegedly teaching that the Abeta peptide develops protease resistance in association with its polymerization into amyloid fibrils. The Examiner asserted that the skilled artisan would have been motivated to modify the methods of Cordell to determine the ability of a candidate substance to inhibit aggregation by assessing the aggregate-prone amyloid protein aggregation as detected by increased protease resistance.

As detailed above, the combination of Cordell, Patino, Hughes, Rieger, Hitzeman, and Chang does not render obvious the method of independent claim 1. Nordstedt provides nothing that supplements the deficiencies of Cordell, Patino, Hughes, Rieger, Hitzeman, and Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claim 16 should also be in condition for allowance.

CONCLUSIONS

Applicant submits that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 17481-004001.

Respectfully submitted,

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